EXCIPIENTS—POWDERS AND SOLID DOSAGE FORMS

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INTRODUCTION

Excipients are the additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients (1). Although excipients are the nonactive ingredients, they are essential in the successful production of acceptable solid dosage forms such as tablets and powders. For example, the lack of filling materials would make it exceedingly challenging, if not impossible, to produce a 1 mg dose tablet of a potent drug.

The following general criteria are essential for excipients (2): physiological inertness; physical and chemical stablility; conformance to regulatory agency requirements; no interference with drug bioavailability; absence of pathogenic microbial organisms; and commercially available at low cost.

In reality, no single excipient would satisfy all the criteria; therefore, a compromise of the different requirements has to be made. For example, although widely used in pharmaceutical tablet and capsule formulations as a diluent, lactose may not be suitable for patients who lack the intestinal enzyme lactase to break down the sugar, thus leading to the gastrointestinal tract symptoms such as cramps and diarrhea. The role of excipients varies substantially depending on the individual dosage form.

EXCIPIENTS IN TABLETS AND CAPSULES

For tablets and capsules, excipients are needed both for the facilitation of the tableting and capsule-filling process (e.g., glidants) and for the formulation (e.g., disintegrants). Except for diluents, which may be present in large quantity, the level of excipient use is usually limited to only a few percent and some lubricants will be required at $<1\%$. Details of the types, uses, and mechanisms of action of various excipients for tablet and capsule production have been discussed at length in other articles in this encyclopedia.[a] The types and functions of excipients for tablet production are summarized in Table 1. Although binders, lubricants, and antiadherents are specific for making tablets, other excipients in Table 1 are also used in capsule production for reasons similar to those for tablets.

It is worth noting that some of these tableting excipients may exert effects in opposition to each other. For example, binders and lubricants, because of their respective bonding and waterproofing properties, may hinder the disintegration action of the disintegrants. In addition, some of these tableting excipients may possess >1 function that may be similar (e.g., talc as lubricant and glidant) or opposite (e.g., starch as binder and disintegrant) to each other. Furthermore, the sequence of adding the excipients during tablet production depends on the function of the excipient. Whereas the diluents and the binders are to be mixed with the active ingredient early on for making granules, disintegrants may be added before granulation (i.e., inside the granules), and/or during the lubrication step (i.e., outside the granules) before tablet compression.

EXCIPIENTS IN FREEZE-DRIED (LYOPHILIZED) POWDERS

Freeze-dried (lyophilized) powders are obtained by the process of freeze-drying (lyophilization), which involves freezing of an aqueous-based drug solution in a glass vial followed by sublimation of the ice in a vacuum (3). Because the process is carried out at low temperatures, it is most suitable for heat-sensitive compounds. Antibiotics, such as cephalosporins, are among the preparations commonly prepared by freeze-drying (4). An interesting finding of excipients in freeze-drying is related to breakage of the glass vial (5). This was observed in excipients, such as mannitol, which would undergo mechanical expansion during warming after fast freezing.

Excipients are used in freeze-drying for various purposes. They act as bulking agents to give a pleasing

[a]See *Tablet Compression*, page 2669; *Tablet Formulation*, page 2701.

Table 1 Summary of types and functions of tableting excipients

Excipient	Functions	Examples
Diluent	To act as a bulking agent or filling material	Sugars, lactose, mannitol, sorbitol, sucrose
		Inorganic salts, primarily calcium salts
		Polysaccharides, primarily microcrystalline celluloses
Binders and adhesives	To hold powders together to form granules for tableting	Sugars, glucose, syrup
		Polymers, natural gums, starch, gelatin or synthetic celluloses, polyvinylpyrrol-pyrrolidone (PVP), poly-methycrylate (Eudragit™)
Glidants	To improve the flow of granules from the hopper to the die cavity to ensure uniform fill for each tablet	Fine silica, magnesium stearate, purified talc
Disintegrants	To facilitate the breakup of a tablet in the gastrointestinal tract	Starch and derivatives (polyplasdone XL)
		Microcrystalline cellulose
		Clays, algins, gums, surfactants
Lubricants	To reduce the friction between the granules and the die wall during compression and ejection of the tableting process	Water-insoluble: metal stearates, stearic acid, talc
		Water-soluble: boric acid, sodium chloride, benzoate and acetate, sodium or magnesium lauryl sulfate Carbowax 4000 or 6000
Antiadherents	To minimize the problem of picking, i.e., portion of the tablet face picked out and adhered to the punch face during tableting	Talc, cornstarch, metal stearates, sodium lauryl sulfate
Colorants	For identification purposes and visual marketing values	Natural pigments
		Synthetic dyes
Flavors and sweeteners	To improve the taste of chewable tablets	Natural, e.g., mannitol
		Artificial, e.g., aspartame

appearance to the freeze-dried products. Buffers are present to control the pH of the products that are stable only within a narrow pH range in solution, both during freezing and the subsequent reconstitution. However, it is important to realize that certain buffers, such as the phosphate buffer, in which $Na_2HPO_4 \cdot H_2O$ crystallizes during freezing, cause a pronounced drop in pH (6). This can lead to deleterious effects on the active ingredients, according to the pH dependence of the product stability. Other excipients that may be present in freeze-dried powders include: solubility enhancers (e.g., surfactants or cosolvents), osmotic agents (e.g., saline and sugars), antioxidants (e.g., ascorbic acid), and preservatives for multiple-injection containers (e.g., benzyl alcohol and chlorobutanol). In addition, freeze-dried biological powders may also contain excipients that function to reduce protein adsorption onto the container surface (e.g., surfactants and albumins) (7). A particularly important use of excipients for therapeutic protein formulations is the stabilization of the protein molecules in the dry state, as discussed later.

Therapeutic Protein Formulations

Therapeutic proteins are usually prepared in liquid formulations or as freeze-dried powders that are to be reconstituted immediately before use. A number of the proteins have been found to be unstable when dried alone, with aggregation being a major problem. It has been found that stability can be greatly improved if the proteins are dried in the presence of certain excipients (8, 9). However, not all excipients that can stabilize protein against aggregation are suitable. Other considerations required of the excipients for use in protein pharmaceuticals include:

Redox reaction potential: reducing sugars such as lactose and sucrose may not be suitable if they react with the protein (e.g., via the lysine residue) resulting in protein glycosylation [e.g., lactosylation of recombinant deoxyribonuclease I by lactose (10)] and other reaction products. However, glycosylation alone may not necessarily be a problem if the glycosylated proteins do not cause toxicity and immunogenicity while maintaining the therapeutic efficacy.

Parenteral use suitability: excipients such as trehalose, which has not been used in any products acceptable by regulatory authorities, may create concerns over toxicity.

Nonparenteral use feasibility: for example, inhalation drug delivery; lactose has been used for marketed aerosol products and hence may be more suitable for inhalation protein formulations.

Table 2 gives some examples of excipients used as stabilizers for proteins in freeze-dried formulations. Among others, saccharides are the most widely used excipients for stabilizing freeze-dried therapeutic proteins. There are exceptions to the need for stabilizing excipients, e.g., recombinant (α-Antitrypsin was stable when freeze-dried alone or with lactose, sucrose, and polyvinylpyrrolidone (11).

The mechanism of the protective effects imparted by the excipients has not been fully elucidated. Empirical observations have pointed to the following contributing factors: formation of a glassy state of the protein–excipient system; crystallinity of the excipients; hydrogen bonding between the excipient and protein molecules; and residual water content.

Glass is an amorphous or noncrystalline solid. It is characterized by the glass transition temperature above which the glassy state softens to the rubbery state. Protein stabilization imparted by excipients can be achieved when the freeze-dried powders are held below the glass transition temperature (T_g) of the protein–excipient systems (i.e., in the glassy state). Of particular relevance to the protein stability is that in the glassy state, the diffusion rate and mobility of the molecules are much less than those in the rubbery state. Thus, any physicochemical reactions leading to protein degradation will be diminished as the protein molecules are "frozen" in the glass formed by the excipients (12).

In contrast to the amorphous excipients, crystalline excipients, such as mannitol, were reported to reduce the stability of proteins (13). Mannitol can be used if the powder is rendered amorphous by the presence of other excipients such as glycine (14). Evidence for protein stabilization by hydrogen bonding has mainly come from the Fourier transformed infrared (FTIR) spectroscopy (15), which provides information on the protein secondary structures. The amide I absorption band (approximately $1600-1700\ cm^{-1}$) of freeze-dried proteins with excipients was found to bear more similarities than the freeze-dried proteins alone to the native proteins in the aqueous environment. This has been explained by sustenance of the native protein structures by protein–excipient hydrogen bonding in the dry powders. However, FTIR measurements were mostly carried out in compressed potassium bromide disks containing the protein. The integrity of the compressed proteins has been largely overlooked (16).

Water affects the stability of proteins by enhancing the mobility of the protein molecules (17). It has been established that an optimal level of water is required to maintain stability of proteins during storage (18). Moisture was known to increase the mobility of the surface groups of protein as measured by solid-state nuclear magnetic resonance spectroscopy (19, 20). The distribution of water between the protein and the excipients in a freeze-dried powder depends on the crystalline or amorphous nature of the excipients (21). For example, if a protein is formulated with an amorphous excipient and stored in a sealed container, water would distribute according to the water affinity of the protein and excipients (21). When the amorphous excipient crystallizes (e.g., because of elevated temperatures), it will expel its sorbed water, which may cause stability problems in the protein (8).

EXCIPIENTS IN POWDER AEROSOL FORMULATIONS

Pharmaceutical inhalation aerosols are widely used for treatment of diseases such as asthma and chronic bronchitis. There are three basic types of aerosol products: the propellant-driven metered-dose inhalers, the dry powder inhalers, and the nebulizers (33). Because of the ozone-depleting and greenhouse effects of the chlorofluorocarbon (CFC) propellants, interest in the dry powder aerosols has risen in recent years.

The main use of excipients in the dry powder inhaler formulations has been to act as carriers for the active ingredients (Table 3). The performance of a dry powder system depends on both the aerosol device and the powder formulation. To generate respirable aerosols, powder formulations must meet two opposing criteria: the particles have to be sufficiently fine (e.g., $<7\ \mu m$) for lung deposition, and yet coarse enough for optimal flow in device (and capsule)-filling and emptying. To achieve this, the drug is blended with coarse inert excipient carriers (34).

Table 2 Some examples of excipients used as protectants for freeze-dried protein and peptide formulations

Protein	Excipients and uses	Reference
Recombinant human growth hormone (rhGH)	Mannitol and glycine as amorphous excipients to prevent human growth hormone (hGH) aggregation. Trehalose as a lyoprotectant, reserves the secondary structure of rhGH.	14
Bovine and human insulins	Dextrin, Emdex^{TM} (spray-dried dextrose) and hydroxypropyl β-cyclodextrin minimized insulin aggregation	22
Recombinant factor IX	Polysorbate 80 as protectant for freezing; sucrose as protectant for drying; histidine as pH buffer; glycine for cake appearance	23
Recombinant human interleukin-6	Aggregation prevented by amorphous trehalose, sucrose or a combination of sucrose, and glycine or mannitol	24
Recombinant human interleukin-1 receptor antagonist	Sucrose, sorbitol, trehalose and alanine as protectants against aggregation and deamidation; mannitol and glycine as bulkingagent; sodium citrate as buffer	25
FK906 tripeptide	Sugars (sucrose, lactose, trehalose, maltose), polymer (dextran) and salts (NaCl, KCl) to modify the glass transition temperatures of the freeze-dried powders	26
Recombinant human albumin	Organic acid excipient molecules with either a carboxyl group or an amino group present at C-1 position completely stabilized rHA against aggregation	27
Lactate dehydrogenase Phosphofructokinase	Polyethylene glycol as protectant for freezing; sugars (mannitol, lactose, trehalose) as lyoprotectants against loss of bioactivity	28
Alkaline phosphatase	Lactose and trehalose maintain activity longer at elevated temperatures than mannitol	29
Recombinant bovine somatotropin, lysozyme	Both the excipient type (sucrose, sorbitol, glycerol) and moisture content affected protein degradation	30
Hemoglobin	Mannitol protected protein from phase separation induced damage during freeze drying	31
Recombinant human factor XIII	Trehalose and sucrose preserved the native dimeric structure of the protein and prevented aggregates formation	32

Table 3 Some examples of excipients used for dry powder aerosols

Active ingredient	Excipient carrier	Reference
Salbutamol sulfate	Lactose (63–90 μm): regular, spray-dried, and recrystallized	34
Budesonide	Lactose (α-monohydrate (<32 μm, 63–90 μm, 125–180 μm)	39
rhDNase	Lactose (50 wt% < 42 and 115 μm) Mannitol (50 wt% < 43 μm) Sodium chloride (50 wt% < 87 μm)	38
Bovine serum albumin–maltodextrin (50–50)	Lactose (α-monohydrate (63–90 μm) Fine particle lactose (76 wt% < 10 μm) Micronized polyethylene glycol 6000 (97.5 wt% < 10 μm)	40
Recombinant human granulocyte-colony stimulating factor-manntiol	Polyethylene glycol 8000 (38–75 μm, 90–125 μm)	41

Thus, the primary reason of using excipient carrier is to enhance flowability of the drug powder. The excipient carriers are large particles which, because of their sizes (>50 μm), would not be inhaled into the lung. They provide surfaces for the fine drug particles to adhere (Fig. 1), forming an interactive powder mix that would have an improved flowability than the drug alone for handling. On dispersion of the powder by air flow, the fine drug particles are detached from the carriers for inhalation. In an ideal drug–carrier system, the adhesion of the drug to the carriers is strong enough to prevent demixing during filling, handling, and storage, but not so strong as to prevent the generation of fine drug particles by detachment from the carrier during inhalation.

Another reason for using excipient carrier is to improve the availability of fine drug particles in the aerosol cloud. Surface texture of excipients appears to play a prominent role. The fine particle fraction of the antiasthmatic drug salbutamol sulfate was significantly higher with the recrystalline lactose as carrier than with regular or spray-dried lactose. The difference was attributed to the lower surface rugosity (roughness) of the recrystalline lactose (35). With another antiasthmatic compound, salmeterol xinofoate, a formulation using lactose carrier produced a higher fine particle fraction than formulations containing sucrose or spray-dried sorbitol (36). The implication is that using a suitable excipient as carrier it is possible to generate the desirable amount of fine drug particles in an aerosol with a minimal inspiratory effort. Recombinant human deoxyribonuclease I (rhDNase), the first therapeutic protein approved by the Food and Drug Administration (FDA) in the United States for inhalation use in the treatment of cystic fibrosis (37), generated a twofold increase in the fine particle fraction in the aerosol when blended with excipients lactose, mannitol, or sodium chloride (38). In this case, the increase was independent of both the type and relative amount of the excipient used.

Besides surface texture, excipient particle size also plays an important role in the fine particle generation as shown by budesonide, where the highest fine particle fraction was obtained with small-sized (<32 μm) lactose as the carrier (39). Additionally, fine particle excipients such as fine lactose or polyethylene glycol were reported to improve the performance of carrier-based protein dry powder aerosols (40). However, there are some cases where carriers improved total powder emission but reduced the percent of active powders in the aerosol (41). To be useful carriers, the excipients must be physically stable. The important physicochemical characteristics for drug carrier selection are discussed in Ref. 42.

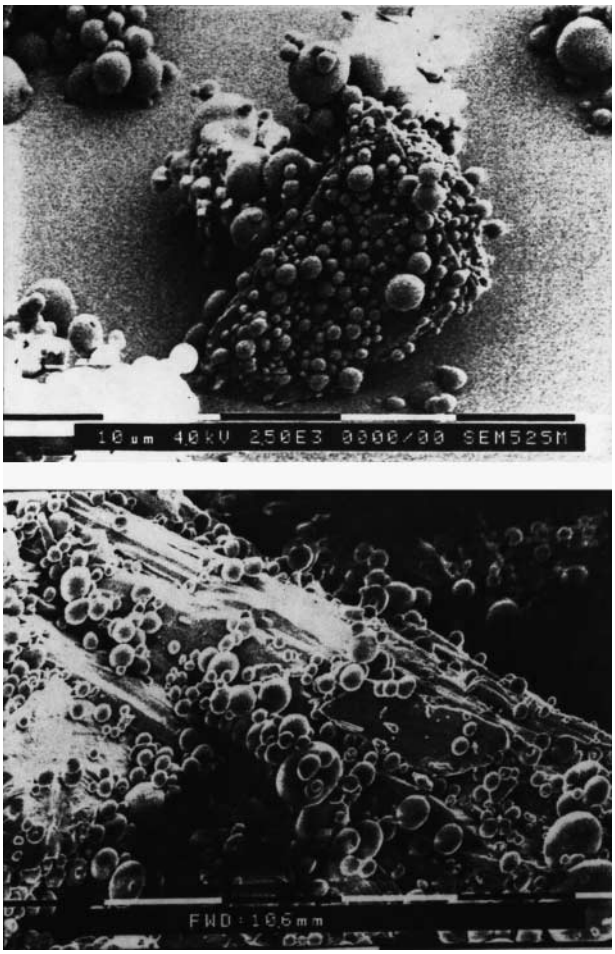

Fig. 1 An example of excipient as carrier for drug particles. Scanning electron micrographs showing adhesion of recombinant human deoxyribonuclease I (rhDNase) particles to lactose (*top*) and mannitol (*bottom*).

In addition to being used as carrier, excipients can enhance the aerosol performance by cospray-drying with the active ingredient. In this case, instead of being external to the drug particles, the excipient exists with the active ingredient in the same particle. For example, using sodium chloride as a crystalline excipient, the fine particle fraction of rhDNase in the aerosol was increased linearly with the amount of excipient present (38). The enhancement was correlated with the degree of crystallinity of the powder in Fig. 2.

As pointed out at the beginning, excipients are not the active ingredients and should be physiologically inert. However, a special use of excipients in dry powder aerosols has been for bronchial provocation testing in asthmatics (43, 44) and for the enhancement of mucociliary clearance in both normal and asthmatic subjects (45, 46). In both cases they acted as the active

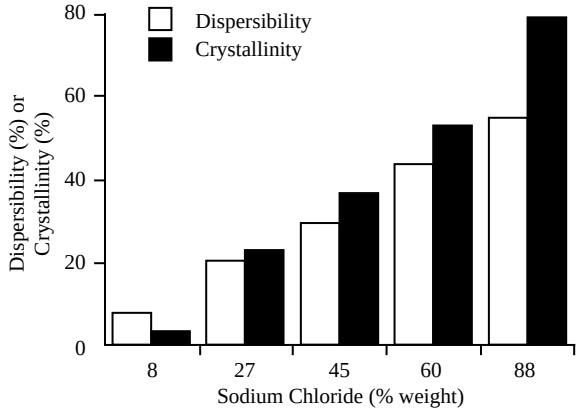

Fig. 2 Relationship between dispersibility (expressed as percent weight of particles less than 7 μm in the aerosol) and crystallinity (by X-ray powder diffraction) of rhDNase powders with different sodium chloride contents. (Adapted from Ref. 38.)

ingredients. The excipients are osmotic agents such as sodium chloride and mannitol. They change the osmolarity of the airway fluid, leading to the physiologic effects of enhanced clearance in the lungs or bronchoconstriction in hyperresponsive subjects.

EXCIPIENTS IN SPRAY-DRIED POWDERS

Spray-drying is a process where a drug solution is atomized to fine droplets followed by evaporation in a stream of warm air to form dry particles (47). The properties of the spray-dried products are controlled by both the process and formulation parameters (48). During the process, the active ingredients are subjected to mechanical shears from atomization and heat stress from the drying air at elevated temperature. Because of the tremendous surface area exposure of the atomized droplets, the drug will also be subjected to degradations such as oxidation and surface denaturation. Excipients can be used as stabilizers or protectants against degradation of the active ingredients. Autoxidation of the analgesic and anti-inflammatory agent aminopyrine was eliminated by excipients such as antioxidants, chelating agents, and clay (49, 50). Denaturation of the model protein (β-Galactosidase was prevented in the presence of trehalose as an excipient (51). Sucrose was found to minimize the degradation product methemoglobin when oxyhemoglobin was spray-dried (52). Recombinant human growth hormone (rhGH), degraded by aggregation resulting from surface denaturation during spray-drying, was successfully stabilized by the surfactant polysorbate 20 (53). Lactose has been found to protect spray-dried rhDNase against aggregation during storage (54, 55). As a cospray-dried excipient, sodium chloride was reported to increase the dispersibility of the spray-dried rhDNase powder to form aerosols for inhalation (38).

Excipients such as colloidal silica have been reported to increase the flow of spray-dried aminopyrine-barbital powders (49). In contrast, formulations of spray-dried salicylic-acid-containing gelatin and polyvinyl alcohol as excipients were less free-flowing (56). Gum arabic and polyvinylpyrrolidone prevented the sublimation of salicylic acid during spray-drying. For vitamin E acetate, the cospray-dried excipients affected both the powder flowability and drug release properties. Hydroxypropyl cellulose improved the drug release properties; Aerosil™ (colloidal silica) enhanced the powder flow. A balance between these two physical parameters was achieved with approximately 6:1 weight ratio of cellulose to Aerosil (57).

Although it does not effectively protect ascorbic acid against oxidative degradation, colloidal silicon dioxide was found to increase the yield of spray-dried powder (58).

For polymorphic compounds, such as sulfa drugs, talc excipients induced polymorphic transformation of sulfamethoxazole during the process of microencapsulation by spray-drying (59).

Particle size and true density of spray-dried sodium salicylate were affected by binder excipients (56). Drug distribution in spray-dried tolbutamide particles was dependent on the disintegrant excipients used. The drug distributed throughout the particles with low-substituted hydroxypropyl cellulose as excipient but only deposited on the surface with pregelatinized corn starch (60).

Excipients like dibutyl phthalate were used as plasticizers for controlled-release microspheres of theophylline and sulfamethazine prepared by spray-drying (61). Likewise, citric acid was used as plasticizer for spray-dried sodium carboxymethyl cellulose and hydroxypropylmethyl cellulose microspheres containing theophylline (62). Excipients were found to affect the release rate of theophylline with citric acid and triethylene citrate giving the slowest and fastest rate, respectively, as compared with polyethylene glycol and glycerin excipients.

EXCIPIENTS IN CONTROLLED RELEASE SOLID DOSAGE FORMS

Polymeric excipients are commonly used for controlled-release formulations either as a coating around a drug core by microencapsulation or as a matrix in which the drug is

embedded. Depending on the release profile requirement, polymeric excipients are traditionally classified as hydrophilic or hydrophobic. Some representative coating materials include water-soluble resins (e.g, gelatin, starch, polyvinylpyrrolidone, water-soluble celluloses), water-insoluble resins (e.g., polymethacrylate, silicones, water-insoluble celluloses), waxes and lipids (e.g., paraffin, beeswax, stearic acid), enteric resins (e.g., shellac, cellulose acetate phthalate) (63). (Further details on polymers for controlled release systems can be found under "Biopolymers for Controlled Drug Delivery" in the first edition of this encyclopedia series.) Here the focus is on some recent applications of excipients in biologicals.

Live rotavirus vaccine was developed for oral delivery to prevent infections by the virus in young children (64). However, incorporation of live rotavirus into poly (DL-lactide-co-glycolide) microspheres or alginate microcapsules was reported to result in a significant loss of rotavirus infectivity. The loss was reduced by stabilization of the rotavirus vaccine with an excipient blend of cellulose, starch, sucrose, and gelatin at a mass ratio of 30:30:30:10 in granules or tablets (64).

Transforming growth factor (TGF)-betal, a cytoprotectant against the toxicity caused by cell cycle-specific drugs, was encapsulated in alginate beads as a potential oral delivery system to release TGF-betal in the gastrointestinal tract. However, the TGF-betal was interacting with alginate, which prevented the release of the protein. Polyacrylic acid, as a polyanion excipient, was used to shield the TGF-betal from interacting with the alginate (65).

Glucose at concentrations >10% was used to achieve adequate reconstitution of freeze-dried biodegradable poly-Σ-caprolactone nanoparticles with conservation of the encapsulated cyclosporin A (66). Glucose and trehalose were also found to be the most efficient cryoprotectors for the lyophilization process, whereas trehalose was used for spray-drying, in the production of solid lipid nanoparticles (67).

Tetanus toxoid (the vaccine for tetanus) encapsulated in polyester microspheres was produced for single-injection immunization (68, 69). The entrapment efficiency of the protein vaccine was significantly improved by coencapsulation with excipients such as trehalose and (γ-Hydro--Hydroxypropyl cyclodextrin. However, these excipients did not impart stabilizing effect on tetanus toxoid. In contrast, bovine serum albumin was found to be the most prominent stabilizer for protein in the body after administration by injection.

It is important to point out that the stabilizing effects of excipients were sometimes reported for the formulations in vitro rather than in the in vivo conditions. However, the degree of retention of the native protein structure in the dry state may not be a general indication of stability for the 'wetted' solid within polymer controlled-release devices in the body. In the case of tetanus toxoid, it was shown that the extent of structural alternations in the presence of 1:5 (gram excipient:gram protein) sodium chloride, sorbitol, or polyethylene glycol did not correlate with stability conferred toward moisture-induced aggregation (70).

Surfactant and polyethylene glycols (PEG) excipients have been used in microencapsulation of macromolecules for various effects. For example, Tween 20, at the critical micelle concentration and at a molar concentration of protein:surfactant of 1:0.018 or larger, was found to increase the encapsulation efficiency of β-Lactoglobuline in poly (DL-Lactide-co-glycolide) microspheres (71). The initial burst release was reduced with increasing Tween 20 concentration, and the effect was attributed to reduction of the number of pores and channels inside the microspheres. For gene therapy, the release of biologicals encapsulated in microspheres can be significantly improved by adding surfactant during microencapsulation, as recently exemplified by the enhancing effect of polyvinyl alcohol on the release of adenovirus from PLGA microspheres (72). PEG 400 has been used to improve the stability of the protein, nerve growth factor (NGF) during the microencapsulation by a double emulsion method. It stabilized the protein by reducing the contact with the organic solvent in the process. Furthermore, the presence of NaCl in the microencapsulation process has been shown to modify the microsphere structures, leading to a reduction of the initial release rate of NGF (73).

EXCIPIENTS AND FORMULATION INCOMPATIBILITY

During formulation design some excipients may be incompatible with the active ingredient or with other excipients. Excipient incompatibility problems are, in fact, widely published and date back to the mid-1950s. For example, as a tableting excipient, lactose could react via its aldehyde group with both primary (1) and secondary (74) amines by the Maillard-type condensation reaction. Sorbitol, another excipient sugar, is hygroscopic at relative humidity >65%, which should thus be avoided during manufacturing. Calcium salts are other widely used tableting excipients. However, calcium carbonate is incompatible with acids or acidic drugs because of the acid–base chemical reaction. Calcium salts are also incompatible with tetracyclines because of the formation

of calcium–tetracycline complexes. Details of reactivities and incompatibilities of individual excipients are given in Ref. 1. Incompatibility attributable to excipients is commonly studied under accelerated testing conditions or using thermal analyses such as differential scanning calorimetry. However, the results of this rapid testing could be misleading and thus of very limited value (75).

Besides direct excipient–drug interactions, excipients can lead to instability of the active ingredient by an indirect role through moisture distribution. Residual water content is known to affect the stability of solid dosage forms and powders (76). Decomposition of cephalothin sodium and benzylpenicillin potassium decomposition in freeze-dried preparation was believed to be partly attributed to the effect of water binding to excipients (4). The degradation rate of cephalothin sodium increased with the water content of excipients corn starch and celluloses (77). The results were correlated with the water mobility in the presence of the excipients (4, 77). A study of the effect of various excipients on the solid-state crystal transformation of the antimalarial compound mefloquine hydrochloride revealed that microcrystalline cellulose promoted the transformation from form E into form D (78). However, methylcellulose, hydroxyethylcellulose, β-Cyclodextrin, crospovidone, and hydrous lactose had no effect. The effect was again explained by the difference in the water uptake behavior by the excipients. Aspirin was formulated with a sugar diluent containing approximately 8% moisture, which did not cause instability problems (79). This was ascribed to the moisture present in the formulation being unavailable to react with the aspirin. The availability of moisture associated with excipients in a formulation can thus be manipulated to control the hydration rate of the active ingredient as in the case of nitrofurantoin, with crystalline lactose giving the fastest and microcrystalline cellulose giving the slowest rate (80). The rate of hydrolysis of methylprednisolone sodium succinate was higher when cofreeze-dried with mannitol than with lactose (81). This correlated with the rate of crystallization of mannitol in the formulation and its subsequent effect on the water distribution in the solid. The stabilizing potency of excipients on recombinant human albumin against aggregation also correlated with the water-sorbing capacity of the excipients (27).

Instability attributable to excipient-mediated water distribution in solids and powders has been explained by excipient physical properties (21, 82–84). Crystalline materials will not uptake moisture until the deliquescent point is reached. In contrast, amorphous excipients will absorb water until their glass transition temperatures fall below the ambient temperature when the mobility of the molecules has increased so much that excipient crystallization will occur to expel the absorbed water from the crystal lattice. Before crystallization, these excipient materials will act as buffers or sorbents to hold the excess moisture which, depending on the water activity, may not be accessible to the active ingredient that is thus be protected from moisture-mediated decomposition. However, when excipient crystallization occurs, the expelled water will become available to react, leading to instability of the drug.

CONCLUSION

Although excipients are the nonactive ingredients, they are indispensable for the successful production of acceptable solid dosage forms. The important roles played by excipients in tablets and capsules, freeze-dried, and spray-dried powders, as well as powder aerosol formulations, were discussed. Some recent applications of excipients in controlled, release formulations for biologicals were also highlighted. Finally, incompatibility problems attributable to excipients were considered with an emphasis on the indirect role of excipients through moisture distribution.

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